REMARKS/ARGUMENTS

Claims 1, 2, 4-11, 21-23, and 26-29 are active. The claims have been revised for clarity and to remove multiple dependencies and employ conventional Markush terminology. New claim 28 tracks claim 4, but is presented in independent form. Claim 27 and new claim 28 are presented as method claims and find support in prior claims 26-27 as well as on page 1 of the specification. The non-elected claims have been cancelled without prejudice to their presentation in a Divisional Application. The Applicants do not believe that any new matter has been added. Favorable consideration of this Amendment and allowance of this application are respectfully requested.

Lack of Unity/Restriction/Election

The Applicants previously elected with traverse Group I. This requirement has been made FINAL. The non-elected claims have been cancelled without prejudice.

Objection

Claims 7-11, 21-22 and 26-27 were objected to as being improperly multiply dependent. This objection is now moot.

Rejection—35 U.S.C. §112, first paragraph

Claims 1-3 and 5-6 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description. The Applicants respectfully submit that this rejection is moot in view of the amendments above.

Amended Claim 1 is now directed to peptides labeled with a radioactive halogen, a positron emitter, which is fluorine ^{18}F and comprising the sequence (I) where amino acids U and B as defined in the Table 1 which previously appeared in claim 3. The amino acids at

positions 7, 14, 38, 62 and 75 are as defined in the sequences SEQ ID NOS: 1 to 14 in the sequence listing.

As disclosed, the present invention concerns peptides directly or indirectly labeled with fluorine ^{18}F, derived from annexin domain 1 which have superior properties in terms of affinity for phospholipids, toxicity, thermodynamic stability and reversibility of their folding processes when compared to prior art peptides such as those disclosed by Montaville et al., 2002, JBC, vol. 277, pages 24684-93.

Thanks to these superior properties and the direct or indirect labeling with a radioactive fluorine ^{18}F, a positron emitter, the peptides of the invention are useful for detecting not only *in vitro* but also *in vivo* apoptotic cells or foci, negatively charged lipids at the surface of the cells, etc.

Claim 1 now specifically describes amino acids at positions 7, 8, 11, 12, 14, 15, 16, 17, 19, 20, 22, 25, 29, 31, 37, 38, 40, 44, 50, 52, 55, 56, 57, 58, 60, 62, 68, 72 and 75. Thus, 29 amino acids of the 75 amino acid residues in this sequence are specifically described by this claim. Moreover, the identities of the remaining amino acid residues are limited to specific groups, for example, the amino acids at positions 59 and 65 must be chosen among the 4 following amino acids Glu, Asp, Lys and Arg. Selection of these amino acids solves the technical problem of the present invention as depicted by the following diagrammatic structure:

As explained at paragraphs [0076] and [0082] of US 2006/0233706, the domain directly or indirectly interacting with the membrane lipids mainly comprises the residues 12, 15, 16, 17, 19, 20, 22, 50, 55, 57, 58, 59, 60 and 65. These residues affect the peptide affinity for lipids and are clearly identified in the peptide sequence in Claim 1.

The stability and more generally the thermodynamic properties of the peptide subject-matter of the present invention mainly depends on the domain called hydrophobic core the residues of which are the residues U and B listed in Table 1. To improve the properties in comparison with annexin, the inventors discovered that it was necessary to choose a suitable combination of hydrophobic residues.

The lower part of the peptide according to the invention includes, in particular, N-terminal and C-terminal segments to be used for various labelings (for example, positioned at the star of the diagram) and/or grafting on various supports.

For surface residues of the peptide according to the invention, other than those mentioned above, there is a certain freedom of choice. It should be noted however that some of these amino acids were set in the peptide sequence of the amended Claim 1 and on the basis of amino acids routinely found in the same position in SEQ ID NO. 1 to 14 of the appended sequence listing.

The peptide sequence as now described by Claim 1 comprises 75 amino acids of which 29 amino acids are identified by the base sequence of formula (I) and by reference to the selections required by Table 1. Thus, nearly 50% of the amino acid sequence of the peptide identified by specific amino acid residues. Moreover, these amino acids are identified at the positions involved in the affinity of the peptide for phospholipids, toxicity, thermodynamic stability and reversibility of their folding processes. Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—35 U.S.C. §112, second paragraph

Claims 1-3 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the cancellation of the prior claims or the amendments above. The claims have been amended to drop the term "derivative", the phrases including "such as" have been removed, and for clarity the Table 1 now appears in claim 1. The variables of U and B limit the variables recited in claim 1 as indicated by the expression "the amino acids U and B of the sequence (I) are chosen according to one of Examples a) to j)".

With respect to " indirect binding", the Applicants respectfully submit that this term would be clear to one of skill in the art when read in light of the specification, see e.g., paragraph [0073] of US 2006/0233706.

Objection/Allowable Subject Matter

The Applicants thank Examiner Gupta for indicating that the subject matter of claim 4 is allowable. Claim 4 is now presented in independent form. Thus, this objection is moot and this claim may now be allowed.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

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